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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JUEDES, AMY E	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,807	TJOA ET AL.	
	Examiner	Art Unit	
	Amy E. Juedes, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *4-7,10-12,16 and 24-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,8,9,13-15 and 17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 2/22/07, are acknowledged.

Claims 1-29 are pending.

2. Claims 4-7, 10-12, 16, 24-29 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1, 3, 8-9, 13-15, 17-23 are being acted upon.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign count0ry or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 14, 17-19, and 23 stand rejected under 35 U.S.C. 102(b) as being anticipated by Sallusto et al., 1994, J. Exp. Med.

As set forth previously, Sallusto teaches a method for generating dendritic cells from peripheral blood mononuclear cells (i.e. monocytic dendritic cell precursors) by culturing in GM-CSF in the absence of additional cytokines (see Table 1). Furthermore, said dendritic cells are immature, as evidenced by their expression of CD11c and MHC, but lack of expression of B7 (see Table 1). Furthermore, the monocytic dendritic cell precursors used to generate the immature dendritic cells were non-activated (i.e. isolated on a Percoll gradient without positive selection or other stimulation- see materials and methods). Additionally, the differentiated dendritic cells were contacted with a bacterial antigen (tetanus toxoid) for a time period sufficient for antigen uptake, as evidence by their ability to stimulate tetanus toxoid specific T cells (see Table 1).

Applicant's arguments and declaration of inventor Bosch filed 2/22/07 have been fully considered, but they are not persuasive.

Applicant has submitted a declaration by inventor Bosch as evidence of the fact that the cells obtained by Sallusto et al. by culture in GM-CSF alone are not dendritic cells. Applicant particularly cites Sallusto et al., who teach that dendritic cells express CD1 and B7, and require IL-4 to maintain the immature antigen presenting state. Thus, Applicant concludes that the GM-CSF cultured cells of Sallusto et al. are not

immature dendritic cells, since they are not disclosed as such, they exhibit equivocal (+/-) expression of B7, and are negative for CD1a.

Sallusto et al. have performed all the steps of the claimed method, and therefore must have inherently obtained immature dendritic cells. Applicant is essentially arguing that Sallusto et al. teach away from using GM-CSF alone to obtain immature dendritic cells. However, arguments that a prior art reference teaches away from the invention or is not recognized as solving the problem solved by the claimed invention, are not germane to a rejection under section 102. In fact, a reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. The question whether a reference "teaches away" from the invention is inapplicable to an anticipation analysis (see MPEP 2131.05). Moreover, it is well established that dendritic cells are a heterogeneous cell population that exist as many different subtypes with different surface phenotypes. Cited merely in response to Applicant's arguments, Lutz et al., 1999 (of record) teach a population of immature dendritic cells that express CD11c, but essentially do not express B7 (see page 81 and 84, in particular). Likewise, WO 03/010292 (of record) teaches that immature dendritic cells are CD11c+ and CD86 (B7) negative (see page 21). Again, in response to Applicant's arguments, the existence of dendritic cell subsets that are negative for CD1a is known in the art (see Freudenthal et al., page 7701, and O'Doherty et al., page 1073, WO 03/010292 pages 27-28, all of record). The cells taught by Sallusto et al. express CD11c, which is well established as a specific marker of dendritic cells. The instant claims are not limited to immature dendritic cells that express CD1a or high levels of B7, and based on the state of the art, a cell that express CD11c, MHC, and B7 at a level of +/- would be considered an immature dendritic cell.

Applicant further argues that an inherency argument cannot be relied upon, because precursor cells taught by Sallusto et al. are not "non-activated", as recited in the instant claims. Applicant particularly argues that the precursor cells can be "activated" by adherence to plastic, and that even if the density gradient isolated precursors of Sallusto et al. are not purified by adhesion, they would adhere to the plastic substrate used for subsequent culture.

The instant specification does not define the term "non-activated". For example, even plastic adherent cells might be considered "non-activated" if they have been cultured in the absence of any direct stimulus. Moreover, the monocytic precursor cells taught by Sallusto et al. were isolated directly from blood by density gradient centrifugation and negative selection without any type of cell stimulation (including adherence to plastic), and can be considered "non-activated". Applicant's argument regarding the asserted subsequent adherence of the precursors to plastic during culture with cytokines is irrelevant, since the instant claims are not limited in this regard.

Applicant further argues that Sallusto et al. do not teach the limitations of claims 17-18, which recite that the dendritic cell precursors are purified by tangential flow filtration. Applicant notes that while an exception to the fact that a reference must teach every limitation of a claim exists in the case of product by process claims, no such exception has been made for "process-by-process" claims.

Applicant's claims are drawn to a method of differentiating dendritic cells employing a dendritic cell precursor (i.e. a method of using a product made by a particular process). Thus, the method by which the product is produced (i.e. a product by process limitation) does not carry patentable weight in the absence of a structurally difference (see MPEP 2113). Applicant has not provided any evidence that a dendritic cell precursor produced by tangential flow filtration is structurally different than the precursors of Sallusto et al.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 3 and 8-9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sallusto et al., 1994, J. Exp. Med, in view of Bernard et al., 1998, Hem. Cell. Ther.

As set forth previously, The teachings of Sallusto are described above.

Sallusto does not culture in a low avidity culture vessel comprising PFTE.

Bernard teaches a method to generate dendritic cells from purified blood monocytes by culturing in a TEFLON^{tm} (i.e. comprising PFTE) bag. Furthermore, Bernard teaches that said method meets good laboratory practice (GLP) procedures necessary for the clinical use of dendritic cells (see pg. 23).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an immature dendritic cell, as taught by Sallusto, using the TEFLON^{tm} culture vessel, as taught by Bernard. The ordinary artisan at the time the invention was made would have been motivated to do so, since Bernard teaches that this method is useful for clinical purposes, since it involves the large scale differentiation of dendritic cells in a culture system that meets GLP procedures (see abstract and pg. 23). Moreover, one of ordinary skill in the art would have a reasonable expectation of success.

Applicant's arguments filed 2/27/07 have been fully considered, but they are not persuasive.

Applicant argues that the cells taught by Sallusto are not "immature dendritic cells", as recited in the instant claims.

However, as noted above, Sallusto et al. have performed the exact steps of the claimed method, and therefore must have obtained immature dendritic cells.

1. Claim 13 and 20-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sallusto et al., 1994, J. Exp. Med, in view of Bosch et al., 2001, J. Invest. Derm., meeting abstract.

As set forth previously, the teachings of Sallusto are described above.

Sallusto does not teach generating immature dendritic cells in serum free medium, nor maturing dendritic cells with IFN-γ and BCG.

Bosch teaches that dendritic cells can be successfully generated in serum free medium, and that dendritic cells can be matured with a combination of INF-γ and BCG. Furthermore, Bosch teaches that dendritic cells are extremely useful for therapeutic purposes, and that the serum free culture medium (in contrast to the FBS containing medium taught by Sallusto) complies with the good manufacturing practice conditions that are required for clinical trials. Additionally, Bosch teaches that maturation with IFN-γ and BCG results in a dendritic cell population that can induce a immune response against a tumor antigen in cancer patients (i.e. a therapeutically useful dendritic cell population).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an immature dendritic cell, as taught by Sallusto, using serum free medium, as taught by Bosch. The ordinary artisan at the time the invention was made would have been motivated to use serum free medium, since Bosch teaches that dendritic cells are extremely useful for therapeutic purposes, and that the serum free culture medium (in contrast to the FBS containing

medium taught by Sallusto) complies with the good manufacturing practice conditions that are required for clinical trials. Furthermore, it would have been obvious to one of ordinary skill in the art to mature the dendritic cells, as taught by Sallusto, with BCG and IFN-γ as taught by Bosch. The ordinary artisan would have been motivated to do so, since Bosch teaches that IFN-γ and BCG are extremely potent maturation agents that result in a dendritic cell population that can induce a immune response against a tumor antigen in cancer patients (i.e. a therapeutically useful dendritic cell population). Moreover, one of ordinary skill in the art would have a reasonable expectation of success, since Bosch teaches the effectiveness of these techniques in the generation of dendritic cells.

Applicant's arguments filed 2/27/07 have been fully considered, but they are not persuasive.

Applicant argues that the cells taught by Sallusto are not "immature dendritic cells", as recited in the instant claims.

However, as noted above, Sallusto et al. have performed the exact steps of the claimed method, and therefore must have obtained immature dendritic cells.

6. Claim 15 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Sallusto et al., 1994, J. Exp. Med, in view of Lewalle et al., 2000, J. Immunol. Methods.

As set forth previously, The teachings of Sallusto are described above.

Sallusto does not teach using a cryopreserved cell population to generate dendritic cells.

Lewalle teaches the generation of dendritic cells from frozen peripheral blood mononuclear cells (see pg. 70). Furthermore, Lewalle teaches that many clinical protocols are based on sequential injections of dendritic cells, and therefore it would be of practical importance to have frozen aliquots of the same peripheral blood mononuclear cells for these purposes (see pg. 70).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an immature dendritic cell, as taught by Sallusto, using frozen peripheral blood mononuclear cells, as taught by Lewalle. The ordinary artisan at the time the invention was made would have been motivated to do so, since Lewalle teaches that many clinical protocols are based on sequential injections of dendritic cells (see pg. 70), and therefore it would be of practical importance to have frozen aliquots of the same peripheral blood mononuclear cells for these purposes.
Furthermore, the ordinary artisan would have had a reasonable expectation of success, since Lewalle teaches that dendritic cells derived from frozen peripheral blood mononuclear cells retain their functional capacity (see pg. 73).

Applicant's arguments filed 2/27/07 have been fully considered, but they are not persuasive.

Applicant argues that the cells taught by Sallusto are not "immature dendritic cells", as recited in the instant claims.

However, as noted above, Sallusto et al. have performed the exact steps of the claimed method, and therefore must have obtained immature dendritic cells.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 8am - 5pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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4/3/09
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